Guidance for Industry

Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Interventional Cardiology Devices Branch
Division of Cardiovascular and Respiratory Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to, Lynette Gabriel, Center for Devices and Radiological Health, HFZ-450, 9200 Corporate Boulevard, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Lynette Gabriel at (301) 443-8243.

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Guidance[1] for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions

I. INTRODUCTION

This guidance document serves a dual purpose. The first purpose is to identify important preclinical tests and clinical design considerations that should be incorporated in the overall evaluation of permanent cardiac pacemaker leads in order to collect data that will document the devices' safety, effectiveness and clinical utility. This guidance may be useful for the preparation of premarket approval applications (PMAs), investigational device exemption (IDE) applications, premarket notifications (510(k)) and master files. The second purpose of the document is to describe a means by which pacemaker lead adaptor devices may comply with the requirement of special controls for class II devices. Designation of this guidance document as a special control means that manufacturers attempting to establish that their device is substantially equivalent to a predicate pacemaker lead adaptor device should demonstrate that the proposed device complies with either the specific recommendations of this guidance or some alternate control that provides equivalent assurances of safety and effectiveness.

Please note that although the remainder of the document refers exclusively to pacing leads, the testing described herein is generally applicable to assessing the safety and effectiveness of pacemaker lead adaptors. FDA acknowledges that nonclinical testing is usually sufficient to support substantial equivalence of a pacemaker lead adaptor in a premarket notification, 510(k) submission.

The development of a guidance document for permanent cardiac pacemaker leads and adaptors is based on the Division of Cardiovascular and Respiratory Devices (DCRD) evaluation of numerous device applications, and the establishment of certain criteria necessary to conduct such evaluations. This is a dynamic document which will be reviewed periodically as device materials, designs and indications for use change and technology improves.

II. GENERAL INFORMATION

The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (the Act) established three regulatory classes for medical devices. The three classes are based on the degree of control necessary to assure that the various types of devices are safe and effective. The amendments define a Class III device as one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury. Permanent pacemaker leads have been classified as Class III devices. Under Section 515 of the Act, all devices placed into Class III are subject to premarket approval requirements. Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices.

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[1] *This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

A preamendments device is one that was in commercial distribution before May 28, 1976, the enactment date of the Medical Device Amendments. Manufacturers of Class III preamendments devices are not required to submit a PMA until 30 months after the promulgation of a final classification regulation or until 90 days after the publication of a final regulation requiring the submission of a PMA, whichever period is later.

At present, no final regulation requiring the submission of PMAs for permanent pacemaker leads has been published.

A postamendment device is one that was first distributed commercially on or after May 28, 1976. Postamendments devices that FDA determines are substantially equivalent to preamendments Class III devices are subject to the same requirements as the applicant's premarket notification submitted in accordance with Section 510(k) of the Act. Postamendments devices determined by FDA to be not substantially equivalent to either preamendments device or postamendments devices classified into Class I or II are "new" devices and fall automatically into Class III. Before such devices can be marketed, they should have an approved premarket approval application or be reclassified into Class I (general controls) or Class II (standards).

Most permanent pacemaker leads reach the market via a Section 510(k) notification. Leads with significantly different technological characteristics and/or indications such that safety and effectiveness could be affected require premarket approval by FDA before they may be commercially distributed (an example of this would be a steroid-eluting lead). Clinical studies in support of a PMA are subject to the investigational device exemptions (IDE) regulations, (refer to 21 CFR 812).

Pacemaker lead adaptors, which were preamandments Class III devices, are now Class II devices.

III. NONCLINICAL TESTING

The following series is intended to identify issues that need to be addressed to qualify a “new” pacemaker lead and to identify some of the non-clinical tests which may be used to support a pacemaker lead submission. Sponsors should examine this listing to determine testing appropriate for their device. For example, if a currently marketed lead is being slightly modified, only data needed to qualify that change needs to be provided. Since new lead designs may experience failure modes not previously seen, this guidance document may not reflect the complete battery of non-clinical testing necessary to qualify all pacing leads/designs. It is the responsibility of the lead manufacturer to define a comprehensive testing methodology for a particular lead design.

A. Biocompatibility

Biocompatibility evaluation depends, in part, on the full characterization of all sterilized device materials in contact with tissue and/or body fluids. In order to accurately identify these materials, the material specifications from the manufacturer, and qualitative and quantitative information concerning all constituent materials used in the manufacturing of the lead should be provided. Furthermore, all protocols, test results and identification of control materials should be provided in order that an

independent evaluation of the study conclusions can be made. Protocols do not need to be submitted if standard methods are utilized (e.g., USP methods) and complete references for the methods are provided.

Biocompatibility testing may not be necessary if a material has a long history of use in currently marketed pacemaker leads. If there is sufficient knowledge about the biocompatibility/toxicity of every constituent of the lead, then it need not be subjected to further biocompatibility tests. It is incumbent upon the device submitter to provide sufficient evidence to establish that further biocompatibility testing is not necessary. A sponsor may submit information and data available in publications or from other legitimate sources which show that the material is non-toxic in tests identical or equivalent to the biological tests listed below. Any changes in formulation, manufacturing or processing (including sterilization) between the tested and submitted products which might affect biocompatibility should be identified.

Biocompatibility testing should be conducted in accordance with ODE book memorandum #G95-1 entitled "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" (from DSMA at 800 899-0381 or 301 827-0111) which includes an FDA matrix that designates the type of testing needed for various medical devices. Implantable pacemaker leads are defined as permanent implant, blood-contacting devices.

The effects of sterilization on device materials and potential leachables, as well as toxic byproducts resulting from sterilization, should be considered when conducting biocompatibility tests. Therefore, testing should be conducted on the sterilized final product and any leachable material from the sterilized final product or representative samples. All test articles should be sterilized using the same procedure that is to be actually used in the manufacturing and sterilization of the final device. The exact chemical analysis of device extracts (eluant or leachable) may be omitted if the extracts are subject to toxicity testing. But, as stated above, the qualitative and quantitative description of all constituent materials in the device before extraction should be provided, and the material specifications for the device should be comprehensive.

If any toxic leachables, by-products, or metabolites exist in the extracts from a sterilized device, the results of the toxicity tests on the extracts should represent the cumulative toxicities from the extracts. Extraction procedures should be rigorous to ensure that the extract toxicity results are representative of the toxicity of the device in actual human use. To provide a safety factor, extractions should be conducted under worst case conditions as compared to those expected from the natural extraction in blood and other human tissues.

The method of extraction should be described in detail. If toxic responses are obtained from the extracts, then chemical analysis of the extract should be performed to address the identity of the toxic compound(s). If a device or its materials are found to be toxic, the sponsor should attempt to find an alternate material that is non-toxic.

B. Animal Studies

The purpose of animal studies is to assess the structural integrity, biostability, electrical performance, biocompatibility, handling characteristics and/or mechanical performance of the fully assembled lead. Animal studies should be designed to closely approximate the intended use of the device in humans. Generally, the canine model is considered appropriate to evaluate pacemaker leads. A sufficient number of animals/leads should be implanted so that valid conclusions may be drawn.

Electrical data should consist of measurement of the following parameters:

- voltage stimulation thresholds at a 0.5 ms pulse width at implant and at appropriate intervals following implant
- R and P wave amplitudes at implant and at appropriate intervals following implant
- pacing impedance at implant and at appropriate intervals following implant
- strength-duration (stimulation threshold versus pulse width)

Possible dislodgments should be documented by radiography and suspected infections at the lead implant site should be assessed by culture and identification of potential pathogens.

At explant, the heart should be excised intact and examined for any lesions and/or trauma. Biocompatibility should be documented via necroscopy and histopathological analysis. Leads should be removed intact and examined for structural integrity and biostability. Biostability of the insulator should be documented by using a state-of-the-art analytical technique(s) e.g., scanning electron microscopy (SEM), infrared (IR) spectroscopy, molecular weight analysis, stress-strain, etc.

A summary should be provided which describes the pre-operative condition of the animals and includes general information on lead handling characteristics, surgical techniques used and a summary of all post mortem findings.

In addition to the tests noted above, steroid-eluting leads should be tested in animals with an appropriate steroid-free control lead, as appropriate, to establish threshold and sensing improvements as well as comparative fibrous tissue encapsulation.

C. Bench Testing

Electrical and mechanical tests should be conducted on components, subassemblies and/or finished leads, as appropriate. All tests should be performed on leads fabricated by representative manufacturing processes and subjected to the final validated sterilization procedures intended for the device. If test samples are subjected to either no sterilization or other sterilization procedures, the rationale for the procedure used should be supplied.

An adequate number of samples should be tested. If sample devices of different lead models are tested, it should be clearly indicated which models were used for each test. The absence of testing on each model should be justified by an analysis demonstrating that the results from the tested devices will accurately predict results for the untested device models.

For any tests that result in unexpected device failure, the failure mode should be completely described. The significance of any tests that result in failure of a device, component, or subassembly to meet a performance specification should be discussed. Corrective actions taken to eliminate or minimize further occurrence of failure should be evaluated via retesting of modified samples.

The performance specifications for all components, subassemblies, and finished devices, and test conditions and acceptance criteria for all tests should be completely explained and justified. Where appropriate, testing should be conducted in an environment simulating *in vivo* conditions. The results of all tests should be reported in a statistically meaningful format, i.e., specification of the number of samples, range of values, mean, standard deviation, and an appropriate confidence interval where applicable. A probability measure that is indicative of the statistical significance of any comparisons made should be provided.

Testing of leads or subassemblies should be performed after sterilization. Testing should include, but not necessarily be limited to, the following, as appropriate:

1. Verify the electrical continuity of each conduction path by measuring the DC resistance. These measurement should comply with the specifications.

2. Measure leakage current during voltage application (after soaking, before drying).

3. Determine the strength of each bond, joint, etc, in the lead (lower 95 percent confidence bound) as well as the composite lead strength. Leads should be subjected to a tensile test which simulates the stress it may experience during the implant procedure as well as after implant. Before pull testing, the lead should be soaked in saline for 10 days to simulate any effects of body fluids on the lead body.

4. For leads that are hermetically sealed at the distal end, verify that the lead is leak-proof when immersed in isotonic saline at 37°C under physiological pressure for a minimum period of ten days.

5. Document the corrosion resistance of all conductors and electrode materials in the condition of the finished lead. Address current pulsing when appropriate.

6. Evaluate the performance of the stylet intended to be used during lead placement. Measure the stylet insertion and removal forces.

7. Fatigue resistance of the conductor(s) should be verified. Intact leads should be used for this testing. Loading conditions that are utilized should be able to be extrapolated to worst-case physiological conditions, i.e., ranges of motion, stresses, etc. Different areas of the lead

are subjected to different stresses; this factor should be taken into consideration in the design of an appropriate test protocol. Test methods designed to accelerate fatigue of conductors should be shown to be able to produce characteristic fracture morphologies that may have been documented previously *in vivo*. Some lead constructions may be amenable to testing in accordance with prEN 45502 Parts 2 & 3 CEN/CENELEC, Active Implantable Medical Devices - Brady and Tachy Lead Tests Draft/Standard. This draft/standard should be carefully reviewed to determine applicability. Fatigue testing of transitions in the distal portion of the lead were not addressed by the draft/standard. Evaluate the fatigue characteristics of lead transition zones located within the heart, where the CEN/CENELEC tests may not be applicable.

8. Connectors intended to be used for joining pulse generators and leads should withstand the mechanical forces that might occur after implantation. Generally, most lead connectors are designed to comply with ISO 5841-3 (IS-1). This standard outlines the appropriate testing for lead connectors. If a connector is labeled as "IS-1" compatible, it should meet all ISO 5841-3 testing and dimensional requirements.

9. Evaluate the performance of the anchoring sleeve packaged with the lead. Testing should assure that the lead will be held securely in place and not damage the lead body when the anchoring sleeve is sutured according to the Instructions for Use.

10. Measure the pressure exerted by lead tip and express in units of pressure.

11. Active fixation leads (extendable/retractable) should be tested to quantify the number of revolutions required to extend and retract the helix. Leads should also be tested to assure the integrity of the helix seal.

Testing specific to **STEROID-ELUTING** leads includes:

1. *In vitro* Elution Rate

   Distal subassemblies containing the drug eluting component should be immersed in an appropriate physiologic solution and analyzed at periodic intervals. The amount of steroid eluted over time should be quantified.

2. Shelf Life

   Aged leads should be analyzed to determine whether the drug composition/quantity varies over the proposed shelf life of the product. The performance of aged leads with respect to steroid performance should be demonstrated.

3. Drug/Matrix Swelling

   The matrix consisting of steroid and housing material as used in the finished device should be examined for the degree of swelling over time. The matrix should also be examined for any evidence of degradation.

D. Insulation Characterization and Biostability

At present, most bradycardia pacemaker leads use either silicone or polyurethane as the insulation material. Polyurethane was introduced in the late 1970's. Overall, the clinical results from several years' experience have been equal or superior to that obtained with silicone. However, a significant rate of insulation failure in certain lead models due to polyurethane degradation have been reported.

If a sponsor is seeking approval to market a polyurethane insulated pacing lead, the following factors will be considered to determine the appropriate level of testing for the lead:

1. Does the sponsor currently market a polyurethane insulated lead which is identical with respect to materials and wall thickness?

2. For bipolar leads (if applicable), are different materials used for the inner and outer insulation?

3. Are the manufacturing parameters, e.g., tubing extrusion, lead assembly, material processing, and quality control consistent with those utilized for other polyurethane leads manufactured by the sponsor?
4. What is the clinical performance (lead survival) of other similarly designed polyurethane leads manufactured by the sponsor? (Discretionary postmarket surveillance study data can be used to address this issue.)

A review of the above factors will be made to determine the need for biostability testing for a particular polyurethane lead model. If, for example, a company currently manufactures polyurethane leads and wishes to market another model using the same material, similar wall thickness, and the lead is manufactured consistent with previous models, then biostability testing may be omitted.

Two scenarios have been identified which may be applicable to a particular lead design:

- the use of a polyurethane which is claimed to be equivalent to Pellethane® 2363
- the use of a new polyurethane material

The testing in each of the above scenarios is outlined in the attached draft test protocols. Please refer to Attachment A (Pellethane® 2363-Equivalent Pacemaker System Polyurethane Components Replacement Protocol) and Attachment B (Pacemaker Flexible Polyurethane Replacement Protocol) for a description of the specific tests recommended. Attachment C (Pacemaker System Rigid Polyurethane Components Replacement Protocol) identifies and defines tests necessary to characterize new polyurethane materials for use in rigid components of pacemaker leads.

IV. CLINICAL TESTING

In many cases, clinical data are not necessary to support market clearance of permanent pacemaker leads. However, if the design of the lead is novel enough or new indications/claims

are being sought for the lead, a clinical trial may be needed. Examples where clinical data may be appropriate include:

- changes to a marketed lead which might alter the handling characteristics
- change in indication from atrial to ventricular pacing
- incorporation of an electrode that has not been approved for use on another lead body

The length of follow-up appropriate in a particular clinical study will be determined by the clinically relevant endpoint that will be measured. It is suggested that sponsors contact FDA early in the process to discuss appropriate trial design and length of follow-up. The pre-IDE process may be a useful mechanism for this discussion. For example, we recommend 30 day follow-up in a study designed only to evaluate handling characteristics. We recommend a randomized trial with a primary effectiveness endpoint in studying the incorporation of a new electrode design/material which could affect the pacing and/or sensing characteristics of the lead. (Note that for purposes of definition, "acute" implantation data refers to data gathered $\leq$ 3 months post-implant; "chronic" data refers to data obtained > 3 months post-implant.)

The success of a clinical trial is based on the overall coordination of three steps: the design of the study; the conduct of the study; and the analysis of the results. The sponsor should carefully consider and execute each step of the trial according to the initial overall study plan.

The clinical study should be ultimately capable of demonstrating the safety and effectiveness of the device in terms of:

- intended patient population
- prescribed, recommended, suggested, and other conditions of use in the labeling or advertising
- probable benefit to health weighed against any probable injury or illness
- reliability of the device (see 21 CFR 860.7(b))

To determine that there is reasonable evidence of the device's safety and effectiveness, FDA must rely on valid scientific evidence to determine that the probable benefits to health from the use of the device for its intended use and conditions of use outweigh any probable risks and that for its intended use and conditions of use the device will provide clinically significant results. This is further defined in 21 CFR 860.7(e)(1) and in the ODE Blue Book Memorandum #P91 - 1 available through DSMA.

A. Clinical Study Design

A detailed protocol for a clinical trial should include:

1 . A well-defined, clear question (hypothesis) or set of questions that are to be answered about the lead by the clinical study.

2. A statement of the study type, i.e., concurrent control, randomized, case control, etc. Historical controls are the most difficult to assure comparability with the study population and will usually entail much more work to validate comparability than concurrent controls. In all cases, the data intended to be used as a control should be identified and comparability discussed with respect to critical study variables including inclusion/exclusion criteria, indications, baseline characteristics, outcome variables, and definitions.

3. A sample size of all study groups calculated to demonstrate that a sufficient number of patients will be enrolled to adequately address the study hypotheses. Sample size is primarily a function of the pre-determined level of significance (i.e., α - the probability of a Type I error) and the power of the study to detect a treatment effect of a predetermined magnitude (i.e., power equals 1 - β where β is the probability of a Type II error). There is some variability in selecting the probability of Type I and II errors. As a general rule, α should not be greater than 0.05 and β should not be greater that 0.20. Any deviation from this range of values should be clearly justified. The greater the difference to be detected between treatment and control groups in the study, the lower the number of subjects needed, provided the α and β remain unchanged. Other factors that need to be considered in calculating the sample size include, for example, the expected loss to
follow-up, the length of the follow-up period and allocation ratio to the treatment groups. It is imperative that the sponsor seek the assistance of a statistician familiar with clinical trial methodology in order to develop the protocol and determine the appropriate number of subjects to be enrolled in the study.

4. A description of the means to eliminate selection bias should be included in the protocol. Sequential screening of all potential subjects for the study, with a record of the patients not enrolled and the reason for non-enrollment is one way of avoiding selection bias.

5. A specification of the outcome variables or clinically relevant endpoints that will be measured to support the study hypotheses. The measure of each primary endpoint should be objective and concisely defined.

6. A specification of all baseline and follow-up assessments consistent with the study objectives. Follow-up assessments should include the allowable time window.

B. Study endpoints

Endpoints commonly used for the evaluation of permanent pacing leads include the following:

1. Effectiveness

   - voltage stimulation thresholds
   - sensing characteristics
   - battery longevity
   - pacing impedances

2. Safety

Lead related adverse events (complications and observations). The following should be addressed regarding complications and observations:

- Complications are lead-related adverse events that are corrected using invasive measures to correct or which result in the loss of a significant device function, e.g., lead dislodgment;

- Observations are lead-related adverse events which are corrected by non-invasive measures, e.g., reprogramming; and

- deaths, all deaths and lead-related deaths

C. Criteria for Lead-Related Complications and Failures

WHEN: The following condition occurs:

- Conductor Failure
- Dislodgment
- Extracardiac Stimulation
- Insulation Breach
- Pacing Impedance less than 200 ohms (describe how impedance was measured)
- Pacing Impedance greater than 3000 ohms or beyond the measuring capabilities of the device (describe how impedance was measured)
- Loss of Capture
- Oversensing
- Perforation
- Undersensing/Loss of Sensing

AND: The condition was not:

- Caused by a pulse generator malfunction or
- Corrected by reprogramming of the pulse generator (except for reprogramming of mode or polarity)

THEN: The occurrence should be reported along with the following interventions/interactions in which the lead was:

- Abandoned Electrically
- Abandoned Surgically
- Modified Electrically
- Modified Surgically

- Removed/Explanted (full or partial)
- Tolerated (based on medical judgment)

Definitions of Terms

Conductor Failure: Visual, electrical, and/or radiographic evidence of mechanical break within the lead conductor (includes connectors, coils, and/or electrodes).

Dislodgment: Radiographic, microdislodgment, electrical or electrocardiographic evidence of electrode displacement from the original implant site or electrode displacement that adversely effects pacing and/or lead performance.

Extracardiac Stimulation: Clinical observation of inadvertent muscle/nerve stimulation other than cardiac muscle or the sensation of subclinical shocks where the pulse generator has been eliminated as a possible reason for the problem.

Implanted Lead: A lead is considered implanted when the surgical incisions are closed.

Insulation Breach: Visual, electrical, or radiographic evidence of a disruption or break in insulation.

Lead Abandoned Electrically: A lead (atrial or ventricular) that remains connected to a pulse generator whose function is disabled through reprogramming in response to either an arrhythmia (e.g., atrial fibrillation) in a lead with normal mechanical and electrical integrity or in response to mechanical of electrical dysfunction of the lead.

Lead Modified Electrically: A lead that remains connected to a pulse generator whose function is altered through reprogramming (e.g., changing from bipolar to unipolar) in response to a problem with the mechanical or electrical integrity of the lead.

Lead Modified Surgically: Any mechanical alteration of the lead (e.g., replacing a connector) in response to a mechanical problem or displacement of the lead. Leads could be modified to accommodate cardiac physiology or to deal with expected evolution (e.g., passage of additional lead length in a growing child).

Loss of Capture: Intermittent or complete failure to stimulate the heart with stimuli delivered outside the refractory period at programmed setting previously effective.

Oversensing: At programmed settings, faulty discrimination between cardiac signals (e.g., ventricular repolarization potential of T wave) or extra cardiac signals (e.g., pacemaker stimuli, skeletal muscle potentials, or electromagnetic signals).

Perforation: Penetration of the lead tip through the myocardium, clinically suspected (microperforation), or confirmed by chest x-ray, fluoroscopy, echocardiogram, intracardiac electrogram, and/or visually.

Removed/Explanted Lead: Any intravascular segment (partial) of a lead or whole lead system that is removed (extracted) or explanted.

Tolerated (Lead Function): When a physician determines that no corrective action is warranted to remedy a lead -related complication or failure.

Undersensing/Loss of Sensing: Intermittent or complete loss of sensing or failure to detect the intended intrinsic cardiac signals (atrial or ventricular) during non-refractory period at programmed settings.

Mortality information presented should include clear definitions of patient death categories and overall mortality rate. All patient deaths should be supported by sufficient documentation.

D. Methods of Lead Safety Analysis

Kaplan-Meier survival analysis for lead related events (complications and observations) or other statistical methods with appropriate justification for the validity of the method proposed should be provided.

E. Steroid Pacing Leads

In 1986, the first steroid pacing leads incorporating dexsamethasone sodium phosphate steroid were approved by FDA. Since that time, safety and effectiveness of this steroid in pacing lead applications has been demonstrated and reported upon extensively in the medical literature. As a result, a randomized clinical trial comparing a steroid version of a particular lead to a non-steroid version may not be appropriate in all cases. Instead, the use of point estimates may be a valid method by which to assess safety and effectiveness. The validity of the point estimate(s) proposed should be discussed with FDA prior to the initiation of a clinical study.

V. POSTMARKET SURVEILLANCE

One of the provisions of the Safe Medical Devices Act of 1990 (SMDA) provided for Discretionary Postmarket Surveillance (DPS) studies. The Food and Drug Administration (FDA) has decided to use this provision to require the submission of additional data about the safety and effectiveness of permanent implanted cardiac pacemaker electrodes (leads). FDA has determined that the legal entity who has received clearance to market through-submission of the premarket notification (510(k)) or premarket approval (PMA) application for a particular lead (hereinafter referred to as sponsor) will have primary responsibility for conducting postmarket surveillance of that lead. All others who are involved in the distribution of these devices will be responsible for ensuring that any data or information in their possession is made available to the sponsor of a DPS protocol. For example, a company may be required to provide the sponsor with information on the material's supplier or sales

and distribution date so that the lead performance may be assessed by the sponsor through patient follow-up.

The “Guidance to Sponsors on the Development of a Discretionary Postmarket Surveillance Study for Permanent Implantable Cardiac Pacemaker Electrodes (Leads)" is available through DSMA. This document provides guidance to sponsors on the design of a study protocol which needs to be submitted to the FDA for approval.

VI. LABELING

Guidance regarding device labeling can be obtained from FDA's publication "Labeling: Regulatory Requirements for Medical Devices" and from ODE's "Device Labeling Guidance G91-1." You may also obtain these documents from DSMA.

Attachment A

Pellethane® 2363-Equivalent Pacemaker System Polyurethane Components Replacement Protocol

Purpose: Identify and define testing to compare the characteristics of proposed polyurethane equivalents from alternate vendors to those of Pellethane® 2363.

Pellethane® 2363 is a well characterized family of rigid and flexible polyurethanes utilized in pacemaker systems since 1980. If the proposed equivalent polyurethanes are shown not to be substantially different on the basis of chemical composition from Pellethane® 2363, (as per I. Material Characterization, below), then the material can be shown to be functionally equivalent to Pellethane® 2363 via this protocol.

Otherwise, the proposed material should be characterized according to Attachment B, Pacemaker Lead Flexible Polyurethane Components Replacement Protocol or Attachment C, Pacemaker System Rigid Polyurethane Components Replacement Protocol. Pellethane® *is a registered trademark of Dow Chemical Company.*

We recommend comparing test results for the new material to the test results of the material being replaced as outlined in the following tables. Also, provide general thermal and processing history of the material samples. Analysis techniques noted are supplied as examples. Comparable methods may be used with appropriate justification. Include an explanation and interpretation of the experimental methodology utilized.

Specimen types in the following tables are abbreviated:
R = resin pellets or American Society for Testing and Materials (ASTM) dog bone.
M = molded piece part exposed to all manufacturing steps (including sterilization).*
E = extruded piece part exposed to all manufacturing steps (including sterilization).*

NOTE: R, M, and E SPECIMENS SHOULD BE APPROPRIATELY CONDITIONED BEFORE PERFORMING TESTS.

* If the molded or extruded piece part geometry can not be adequately evaluated per this protocol, a suitable alternative geometry (e.g., ASTM dog bone), subjected to all manufacturing steps (including sterilization), can be substituted.

I. Material Characterization

A. Composition	R	M	E	ASTM Standard Test Method
	x			-

The following information on composition is typically supplied in a FDA Master File. If a Master File is not accessible, the material supplier/processor should supply information

identifying potentially toxic components. We recommend providing all of the following information in the 510(k).

- Complete formulation information including precursor materials. solvents, catalysts, curing agents, reinforcing agents, crosslinking agents, etc.
- Composition reaction ratios
- Catalyst ratio
- Any relevant literature and patents describing the formulation and characterization of the replacement material

B. Mechanical	R	M	E	ASTM Standard Test Method
Hardness, Durometer Shore A or D	x			D2240
Specific Gravity	x			D792
Ultimate Tensile Strength, psi	x	x	x	D412 or D1708
Ultimate Elongation, %	x	x	x	D412 or D1708
Modulus, psi	x	x	x	D412 or D1708
Tear Strength, Die C, pli *(not required for rigid materials)*	x			D624
Melt Index, grams/10 min				D1238

C. Electrical	R	M	E	ASTM Standard Test Method
Dielectric Strength	x		x	D3755 or D149

D. Chemical	R	M	E	ASTM Standard Test Method
M_w M_n M_w/M_n (GPC)	x	x	x	D3593
Surface Analysis (ATR-FTIR)	x	x	x	-
Tg (DMA or DSC)	x	x	x	E1356, D3418, D5023 or 5026
Thermal Stability (TGA)	x	x	x	-
Trace Metals Analysis (AA)	x	x	x	F1372

Report concentrations of Pb, Cu., Sn, Sb, Hg, As. Cd, Ba, Mg, Se, Si, and compare to concentrations reported for Pellethane® 2363.

II. Biocompatibility

Perform Biocompatibilty testing per ***ISO 10993-1 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.*** Consider ***ISO 10993-12 Biological Evaluation of Medical Devices Part 12: Sample Preparation and Reference Materials*** in the preparation of samples.

KEY

AA	Atomic Absorption
As	Arsenic

ATR-FTIR	Attenuated Total Reflectance FTIR
Ba	Barium
Cd	Cadmium
Cu	Copper
DMA	Dynamic Mechanical Analysis
DSC	Differential Scanning Calorimetry
FTIR	Fourier Transformation Infrared spectroscopy
GPC	Gel Permeation Chromatography
Hg	Mercury
M_w	Weight Average Molecular Weight
M_n	Number Average Molecular Weight
M_w/M_n	Molecular Weight Polydispersity
Mg	Magnesium
Pb	Lead
Sb	Antimony
Se	Selenium
SEM	Scanning Electron Microscopy
Si	Silicon
Sn	Tin
Tg	Glass Transition Temperature
TGA	Thermal Gravimetric Analysis

Specified ASTM Standard Test Methods

D 149 Dielectric Breakdown Voltage and Dielectric Strength of Solid Electrical Insulation Materials at Commercial Power Frequencies.

D 412 Vulcanized Rubber and Thermoplastic Rubbers and Thermoplastic Elastomers Tension.

D 624 Tear Strength of Conventional Vulcanized Rubber and Thermoplastic Elastomers.

D 792 Density and Specific Gravity (Relative Density) of Plastics by Displacement.

D 1238 Flow Rates of Thermoplastics by Extrusion Plastometer.

D 1708 Tensile Properties of Plastics by Use of Microtensile Specimens.

D 2240 Rubber Property - Durometer Hardness.

D 3418 Transition Temperature of Polymers by Thermal Analysis.

D 3593 Molecular Weight Averages and Molecular Weight Distribution of Certain Polymers by Liquid Size Exclusion Chromatography (Gel Permeation Chromatography - GPQ Using Universal Calibration. Using DMF solvent and polystyrene standard.

D 3755 Dielectric Breakdown Voltage and Dielectric Strength of Solid Electrical Insulating Materials Under Direct-Voltage Stress.

D 5023 Measuring the Dynamic Mechanical Properties of Plastics Using Three Point Bending.

D 5026 Measuring the Dynamic Mechanical Properties of Plastics in Tension.

E 1356 Glass Transition Temperatures by Differential Scanning Calorimetry or Differential Thermal Analysis.

F 1372 Scanning Electron Microscope (SEM) Analysis of Metallic Surface Condition for Gas Distribution System Components.

Attachment B

Pacemaker Lead Flexible Polyurethane Components Replacement Protocol

Purpose: Identify and define testing to characterize new polyurethane materials for use in flexible components of pacemaker leads.

We recommend comparing test results for the new material to the test results of the material being replaced as outlined in the following tables. Also, provide general thermal and processing history of the material samples. Analysis techniques noted are supplied as examples. Comparable methods may be used with appropriate justification. Include an explanation and interpretation of the experimental methodology utilized.

Specimen types in the following tables are abbreviated:
R = resin pellets or ASTM dog bone.
M = molded piece part exposed to all manufacturing steps (including sterilization).*
E = extruded piece part exposed to all manufacturing steps (including sterilization).*

NOTE: R, M, and E SPECIMENS SHOULD BE APPROPRIATELY CONDITIONED BEFORE PERFORMING TESTS.

* If the molded or extruded piece part geometry can not be adequately evaluated per this protocol, a suitable alternative geometry (e.g., ASTM dog bone), subjected to all manufacturing steps (including sterilization), can be substituted.

I. Material Characterization

A. Composition	R	M	E	ASTM Standard Test Method
	x			-

The following information on composition is typically supplied in a FDA Master File. If a Master File is not accessible, the material supplier/processor should supply information identifying potentially toxic components. We recommend providing all of the following information in the 510(k).

- Complete formulation information including precursor materials. solvents, catalysts, curing agents, reinforcing agents, crosslinking agents, etc.
- Composition reaction ratios
- Catalyst ratio
- Any relevant literature and patents describing the formulation and characterization of the replacement material

B. Mechanical	R	M	E	ASTM Standard Test Method
Hardness, Durometer Shore A or D	x			D2240
Specific Gravity	x			D792
Ultimate Tensile Strength, psi	x	x	x	D412 or D1708
Ultimate Elongation, %	x	x	x	D412 or D1708
Modulus, psi	x	x	x	D412 or D1708
Tear Strength, Die C, pli	x			D624
Melt Index, grams/10 min				D1238

C. Electrical	R	M	E	ASTM Standard Test Method
Dielectric Strength	x		x	D3755 or D149

D. Chemical	R	M	E	ASTM Standard Test Method
M_w M_n M_w/M_n (GPC)	x	x	x	D3593
Surface Analysis (ATR-FTIR)	x	x	x	-
Tg (DMA or DSC)	x	x	x	E1356, D3418, D5023 or D5026
Thermal Stability (TGA)	x	x	x	-
Trace Metals Analysis (AA)	x	x	x	F1372

Report concentrations of Pb, Cu., Sn, Sb, Hg, As. Cd, Ba, Mg, Se, Si, and compare to concentrations reported for Pellethane® 2363.

II. In-Vivo Device Testing

Note : If acceptable accelerated testing protocols are available, abbreviated testing may be conducted per section II. B. Alternative Submission Strategy. Acceptable accelerated testing should be supported by documentation that demonstrates that the in-vitro testing can reliably predict in-vivo performance.

A. Submission Strategy

- Implant leads in animal hearts to obtain data on 20 leads at the end of 2 two years
- Historical or other suitable controls

B. Alternative Submission Strategy

- Implant leads in animal hearts with intent of obtaining data on 20 leads after six months
- Historical or other suitable controls
- Accelerated Testing - ESC test[1,2] and MIO test[3]

Note : If the test material performs equivalent or better, i.e., <u>better being a lower incidence of failures</u>, than the negative control, and the positive control shows noticeable degradation, then the test material has demonstrated acceptable biostability.

1. *Experimental conditions should be set so that the positive control shows a failure incidence (rate) significantly greater than that expected by pure chance for 20 samples.*

2. *The negative control, should be chosen so that its failure incidence (rate) is significantly less than the positive control failure incidence under the same experimental conditions. Otherwise, the negative control is not really a negative control, but just another positive control.*

Animal testing should include the following biocompatibility/biostability testing. Perform the following tests regardless of which submission strategy is used. Compare properties of explanted polymer samples to those of non-implanted controls.

Complete post-mortem on all animals to include (provide histopathology when abnormalities are observed):

- Heart
- Liver
- Lungs
- Spleen
- Bone marrow
- Kidneys

Thorough visual inspection of polymer using light microscopy.

Thorough analysis, where practical, of anomalous areas on polymer. Anomalous areas should include:

- Discoloration
- Cracks
- Fissures
- Surface irregularities
- Holes
- Thinning
- Bubbles
- Bumps

Chemical Properties	R	M	E	ASTM Standard Test Method
Photomicrography		x	x	-
M_w, M_n, M_w/M_n (GPC)		x	x	D3593
Surface Analysis (ATR-FTIR)		x	x	-
Tg (DMA or DSC)		x	x	E1356, D3418, D5023 or D5026

Mechanical Properties	R	M	E	ASTM Standard Test Method
Ultimate Tensile Strength, psi		x	x	D412 or D1708
Ultimate Elongation, %		x	x	D412 or D1708
Modulus, psi		x	x	D412 or D1708

III. Biocompatibility.

A. Perform Biocompatibilty testing per *ISO 10993.1 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.* Consider **ISO *10993-12 Biological Evaluation of Medical Devices Part* 12 : Sample *Preparation and Reference Materials*** in the preparation of samples.

KEY:

AA	Atomic Absorption
As	Arsenic
ATR-FTIR	Attenuated Total Reflectance FTIR
Ba	Barium
Cd	Cadmium
Cu	Copper
DMA	Dynamic Mechanical Analysis
DSC	Differential Scanning Calorimetry
ESC	Environmental Stress Cracking (oxidation)
FTIR	Fourier Transformation Infrared spectroscopy
GPC	Gel Permeation Chromatography
Hg	Mercury
M_w	Weight Average Molecular Weight
M_n	Number Average Molecular Weight
M_w/M_n	Molecular Weight Polydispersity
Mg	Magnesium
MIO	Metal Ion Oxidation (auto-oxidation)
Pb	Lead
Sb	Antimony
Se	Selenium
SEM	Scanning Electron Microscopy
Si	Silicon
Sn	Tin
Tg	Glass Transition Temperature
TGA	Thermal Gravimetric Analysis

Specified ASTM Standard Test Methods

D 149 Dielectric Breakdown Voltage and Dielectric Strength of Solid Electrical Insulation Materials at Commercial Power Frequencies.

D 412 Vulcanized Rubber and Thermoplastic Rubbers and Thermoplastic Elastomers Tension.

D 624 Tear Strength of Conventional Vulcanized Rubber and Thermoplastic Elastomers.

D 792 Density and Specific Gravity (Relative Density) of Plastics by Displacement.

D 1238 Flow Rates of Thermoplastics by Extrusion Plastometer.

D 1708 Tensile Properties of Plastics by Use of Microtensile Specimens.

D 2240 Rubber Property - Durometer Hardness.

D 3418 Transition Temperature of Polymers by Thermal Analysis.

D 3593 Molecular Weight Averages and Molecular Weight Distribution of Certain Polymers by Liquid Size Exclusion Chromatography (Gel Permeation Chromatography - GPC) Using Universal Calibration. Using DMF solvent and polystyrene standard.

D 3755 Dielectric Breakdown Voltage and Dielectric Strength of Solid Electrical Insulating Materials Under Direct-Voltage Stress.

D 5023 Measuring the Dynamic Mechanical Properties of Plastics Using Three Point Bending.

D 5026 Measuring the Dynamic Mechanical Properties of Plastics in Tension.

E 1356 Glass Transition Temperatures by Differential Scanning Calorimetry or Differential Thermal Analysis.

F 1372 Scanning Electron Microscope (SEM) Analysis of Metallic Surface Condition for Gas Distribution System Components.

REFERENCES:

1. MacGregor, D.C., L. Pinchuk, M.C. Esquivel, J.B. Martin, Jr. and G.J. Wilson, "Corethane ™ as a Substitute for Pellethane ® for Pacemaker Lead Insulators," PACE 14:694(1991).

2. Stokes, K., Urbanski, P. and Cobian, K., "New Test Methods for the Evaluation of Stress Cracking and Metal Catalyzed Oxidation in Implanted Polymers." In H. Planck, et al (eds.), Polyurethanes in Biomedical Engineering II, Amsterdam, Elsevier, 109-128, 1987.

3. Stokes, K., Urbanski, P. and Upton, J. "The in vivo Auto-oxidation of Polyether Polyurethane by Metal Ions." J. Biomaterials Science, Polymer Edition, 1(3), 207-230, 1990.

Atttachment C

Pacemaker System Rigid Polyurethane Components Replacement Protocol

Purpose : Identify and define testing to characterize new polyurethane materials for use in rigid components of pacemaker systems.

We recommend comparing test results for the new material to the test results of the material being replaced as outlined in the following tables. Also, provide general thermal and processing history of the material samples. Analysis techniques noted are supplied as examples. Comparable methods may be used with appropriate justification. Include an explanation and interpretation of the experimental methodology utilized.

Specimen types in the following tables are abbreviated:
R = resin pellets or ASTM dog bone.
M = molded piece part exposed to all manufacturing steps (including sterilization).*
E = extruded piece part exposed to all manufacturing steps (including sterilization).*

NOTE: R, M, and E SPECIMENS SHOULD BE APPROPRIATELY CONDITIONED BEFORE PERFORMING TESTS.

* If the molded or extruded piece part geometry can not be adequately evaluated per this protocol, a suitable alternative geometry (e.g., ASTM dog bone), subjected to all manufacturing steps (including sterilization), can be substituted.

I. Material Characterization

A. Composition	R	M	ASTM Standard Test Method
	x		-

The following information on composition is typically supplied in a FDA Master File. If a Master File is not accessible, the material supplier/processor should supply information identifying potentially toxic components. We recommend providing all of the following information in the 510(k).

- Complete formulation information including precursor materials. solvents, catalysts, curing agents, reinforcing agents, crosslinking agents, etc.
- Composition reaction ratios
- Catalyst ratio.
- Any relevant literature and patents describing the formulation and characterization of the replacement material.

B. Mechanical	R	M	ASTM Standard Test Method
Hardness, Durometer Shore A or D	x		D2240
Specific Gravity	x		D792
Ultimate Tensile Strength, psi	x	x	D412 or D1708
Ultimate Elongation, %	x	x	D1708
Modulus, psi	x	x	D412 or D1708
Melt Index, grams/10 min			D1238

C. Electrical	R	M	ASTM Standard Test Method
Dielectric Strength	x		D3755 or D149

D. Chemical	R	M	ASTM Standard Test Method
M_w M_n M_w/M_n (GPC)	x	x	D3593
Surface Analysis (ATR-FTIR)	x	x	-
Tg (DMA or DSC)	x	x	E1356, D3418, D5023 or D5026
Thermal Stability (TGA)	x	x	-
Trace Metals Analysis (AA)	x	x	-

Report concentrations of Pb, Cu., Sn, Sb, Hg, As. Cd, Ba, Mg, Se, Si, and compare to concentrations reported for Pellethane® 2363.

II. In-Vivo Device Testing

Submission Strategy

- Animal testing as applicable to the finished product
- Historical or other suitable controls

III. Biocompatibility.

Perform Biocompatibilty testing per ***ISO 10993-1 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing***. Consider ***ISO 10993-12 Biological Evaluation of Medical Devices Part 12 : Sample Preparation and Reference Materials*** in the preparation of samples.

KEY

AA	Atomic Absorption
As	Arsenic
ATR-FTIR	Attenuated Total Reflectance FTIR
Ba	Barium
Cd	Cadmium
Cu	Copper
DMA	Dynamic Mechanical Analysis
DSC	Differential Scanning Calorimetry

FTIR	Fourier Transformation Infrared spectroscopy
GPC	Gel Permeation Chromatography
Hg	Mercury
M_w	Weight Average Molecular Weight
M_n	Number Average Molecular Weight
M_w/M_n	Molecular Weight Polydispersity
Mg	Magnesium
Pb	Lead
Sb	Antimony
Se	Selenium
SEM	Scanning Electron Microscopy
Si	Silicon
Sn	Tin
Tg	Glass Transition Temperature
TGA	Thermal Gravimetric Analysis

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